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A new predictor for indicating clinical severity and prognosis in COVID-19 patients: Frontal QRS-T angle

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Title: A New Predictor for Indicating Clinical Severity and Prognosis in COVID-19 Patients: Frontal QRS-T Angle

Brief Title: Frontal QRS-T Angle Values Of Patients With COVID-19

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ABSTRACT

Objective: COVID-19; It spread rapidly around the world and led to a global pandemic. Indicators of poor prognosis are important in the treatment and follow-up of COVID-19 patients and have always been a matter of interest to researchers. The aim of this study was to investigate the relationship between frontal QRS-T angle values and clinical severity and prognosis in COVID-19 patients.

Methods: This prospective case-control study was conducted with 130 COVID-19 patients whose diagnosis was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) and 100 healthy controls. The CURB-65 score was used as the clinical severity score.

Results: A total of 130 patients and 100 healthy controls were included in the study. When the patient and control groups were compared a significant difference was found between QT (378.07±33.75 vs. 368.63±19.65, p<0.001) , QTc (410.75±28.19 vs. 403.68±11.70, p<0.001) , QRS time (95.04±21.67 vs. 91.42±11.08, p<0.001) and frontal QRS-T angle (36.57±22.86 vs. 22.72±14.08, p<0.001). According to clinical severity scoring, QT (370.27±25.20 vs. 387.75±40.19, p=0.003), QTc (402.18±19.62 vs. 421.48±33.08, p<0.001), frontal QRS-T angle (32.25 ±18.79 vs. 41.94±26.27) , p=0.016) parameters were found to be significantly different. Age (odds ratio [OR], 1.201; 95% confidence interval [CI], 1.111-1.298; p<0.001) and frontal QRS-T angle ([OR], 1.040; 95% [CI], 1.015-1.075; p =0.003) values were found to be an independent predictor for the severity of the disease. Frontal QRS-T angle ([OR], 1.101; 95% [CI], 1.030-1.176, p=0.004), and CRP ([OR], 1.029; 95% [CI], 1.007-1.051; p=0.01) parameters were found to be independent predictors for the mortality of the disease. As a mortality indicator for the frontal QRS-T angle of ≥ 44.5°, specificity and sensitivity were 93.8% and 84.2%, respectively.

Conclusion: Frontal QRS-T angle can be used as a reproducible, convenient, inexpensive, new and powerful predictor in determining the clinical severity and prognosis of COVID-19 patients.

Key-words: COVID-19, Mortality, Frontal QRS-T angle, QT, QTc, Ventricular Arrhythmia

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Introduction

Since it was first reported in Wuhan, China on December 31, 2019, the novel coronavirus (COVID-19) has spread rapidly around the world, leading to a global pandemic [1]. The clinical spectrum of COVID-19 ranges from asymptomatic, mild or moderate respiratory infections to severe cases who develop Acute Respiratory Distress Syndrome (ARDS) or multiple organ dysfunctions resulting in death [2]. Despite the advances in vaccine and drug studies, the spread of the disease and mortality are still at high rates. According to the data of the World Health Organization, as of June 18, 2021, a total of 177,108,695 COVID-19 cases and 3,840,223 deaths have been reported worldwide [3].

Indicators of poor prognosis are important in the treatment and follow-up of COVID-19 patients and have always been a matter of interest to researchers. In previous studies, many factors such as advanced age, Diabetes Mellitus (DM), Hypertension (HT), Chronic Renal Failure (CRF), Chronic Lung Disease (For example, COPD), and immunosuppression have been associated with poor prognosis [4]. In addition, laboratory parameters such as high D-dimer level, high C-reactive protein (CRP), high white blood cell (WBC) and lymphopenia have been reported to be indicators of poor prognosis [5,6]. It has also been shown that cardiovascular complications such as myocarditis, heart failure, cardiomyopathy, myocardial infarction, venous thromboembolism and arrhythmia may occur in patients with COVID-19. These complications are reported to be indicators of poor prognosis [7].

Despite all the advances in diagnostic tests and treatments in cardiology, electrocardiography (ECG) remains one of the best methods for detecting cardiovascular diseases. Various symptoms and findings can be seen on surface ECG before the cardiovascular disease findings develop clearly [8]. Previous studies examined the relevance of electrocardiography (ECG) in COVID-19 patients. In these studies, it was reported that many changes such as

supraventricular tachycardia, malignant ventricular arrhythmia, bradycardia, atrioventricular block, ST segment, T wave and QRS complex abnormalities and QT prolongation can be observed in COVID-19 patients [9].

Frontal QRS-T angle is a relatively new indicator showing ventricular depolarization heterogeneity and it may be an indicator of ventricular arrhythmia [8,10]. To the best of our knowledge, there is no study in the literature investigating frontal QRS-T angle values in COVID-19 patients. Therefore, the aim of this study was to investigate the relationship between frontal QRS-T angle values and clinical severity and prognosis in COVID-19 patients.

Methods

This prospective case-control study was conducted with 130 COVID-19 patients whose diagnosis was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) and 100 healthy controls. The control group consisted of people who were similar to the patient group in terms of demographic characteristics and comorbid factors. Ethical permission for the study was obtained from the local ethics committee. The study was carried out in Samsun Gazi State Hospital as a single center study. All patients over the age of 18 whose diagnosis was confirmed by RT-PCR and routine laboratory examination was requested were included in the study. Patients who had previous history of drug use that increased the frontal QRS-T angle value, patients who were previously diagnosed with COVID-19 and received treatment for COVID-19, had history of cardiac arrhythmia, were under the age of 18, had negative or suspicious RT-PCR results, and whose routine laboratory tests were not performed were excluded from the study.

The study was explained in detail to the patients who applied to the COVID-19 clinic of our hospital and met the appropriate criteria for the study. Written consent was obtained from all

patients. Demographic findings, admission symptoms, vital parameters, comorbid factors and prognostic status of the patients were recorded. The 12 lead ECGs of the patients were taken at the time of admission to the emergency department. Routine blood tests and routine imaging tests were performed on these patients. Treatment, follow-up and discharge of the patients were carried out according to the current COVID-19 diagnosis and treatment guideline in Turkey.

In previous studies, it was reported that a cut-off value of ≥2 in CURB-65 score *has high sensitivity and specificity for demonstrating clinical severity and prognosis of COVID-19 patients [11,12]. In the present study, the CURB-65 score was used as the clinical severity score. Patients were divided into two groups as CURB-65 <2 (low risk) and CURB-65 ≥2 (high risk) [11].*

ECG Measurements:

A 12-lead surface ECG was performed for all patients with a paper velocity of 25 mm/s and an amplitude of 10 mm/mV. All ECGs were transferred to the digital platform and measurements were made under magnification to reduce calculation errors. ECG records were analyzed by two independent experienced cardiologists. QRS time was calculated from the beginning until the end of the QRS complex, and the QT interval was measured from the beginning of the QRS complex to the end of the T wave. The corrected QT interval (QTc) was calculated according to Bazett's formula: QTc = QT / √RR. Frontal QRS-T angle was obtained from automated reports of ECG recordings.

Statistical analysis:

Statistical Program for Social Sciences 20 (IBM SPSS, Chicago, IL, USA) was used for all statistical calculations. Kolmogorov-Smirnov test was used to check whether the data were normally distributed. Continuous variables were expressed as mean ± SD or median

(interquartile range) and compared with Student's t or Mann-Whitney U tests according to normality. Categorical variables were expressed as percentages and numbers and compared with the Chi-square test. Univariate regression analysis was performed to identify possible risk factors affecting prognosis. In addition, multivariate linear regression analysis was performed to identify independent predictors of prognosis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum threshold value of frontal (QRS-T) angle level for predicting prognosis in patients with COVID-19. $p < 0.05$ was accepted as statistically significant in all analyses.

Results

A total of 130 patients (72 women, mean age: 53.44±12.38) and 100 healthy controls (62 women, mean age 51.39±12.70 years) were included in the study. When the comorbid factors of the patients were examined, it was found that 10% of the patients had DM, 9.23% had chronic respiratory disease, and 9.23% had heart failure. 15.38% of the patients were smokers. When the patients were evaluated according to their admission symptoms, 61.54% had shortness of breath, 45.38% had myalgia fatigue, and 41.54% had cough. 55.38% of the patients had a Curb-65 score of '0-1'. 21.53% of the patients were treated in the intensive care unit and 12.30% died. Demographic data and basic clinical characteristics of the patients are shown in Table.1.

When the patient and control groups were compared a significant difference was found between systolic blood pressure (SBP) (131 ± 21:50 vs. 126.95 ± 13.96, p <0.001), Glucose (147.17 ± 87.62' vs. 107.06 ± 21:28, p <0.001), WBC (8.65 ± 4.89 vs. 7.98 ± 2.44, p <0.001), urea (44.04 ± 33.23 vs. 28.20 ± 11:33, p <0.001), Creatinine (0.90 ± 0.40 vs. 0.69 ± 0.19, p <0.001), CRP (54.55 ± 67.86 vs. 0.60 ± 1.11, p <0.001) , QT (378.07±33.75 vs. 368.63±19.65, p<0.001) , QTc (410.79±28.19 vs. 403.68±11.70, p<0.001) , QRS time (95.04±21.67 vs. 91.42±11.08, p<0.001) , and frontal QRS-T angle (36.57±22.86 vs.

22.72±14.08, p<0.001) . The comparison of patient and control groups in terms of vital signs, basic laboratory findings and ECG parameters is shown in Table 2.

QT/QTc and f(QRS-T) angle values of the patients were compared according to the CURB-65 score. (Group 1: CURB-65 <2, Group 2: CURB-65 ≥*2)* . A significant difference was found in *QT (* 370.27±25.20 vs. 387.75±40.19, p=0.003) , QTc (402.18±19.92 vs. 421.48±33.08, p<0.001), *frontal QRS-T angle* (32.25 ±18.79 vs. 41.94±26.27, p=0.016) parameters between the groups. When QT/QTc and *frontal QRS-T angle* parameters were compared between patients who recovered and deceased patients, a significant difference was found only between the *frontal QRS-T angle* values (34.22±21.91 vs. 53.31±23.19, p=0.002). The comparison of these groups is shown in Table 3.

According to Univariate logistic regression analysis; age, *frontal QRS-T angle* and Crp values were found to be possible predictors of clinical severity. In multivariate logistic regression analysis; age (odds ratio [OR], 1.201; 95% confidence interval [CI], 1.111-1.298; p<0.001) and frontal QRS-T angle ([OR], 1.045, 95% [CI], The values of 1.015-1.075; p=0.003) were found to be independent predictors for disease severity. The logistic regression analysis results related to disease severity are shown in Table 4.

According to Univariate regression analysis; age, *frontal QRS-T angle*, Crp and smoking status were found to be possible independent predictors of mortality. In multivariate logistic regression analysis; frontal QRS-T angle ([OR], 1.101; 95% [CI], 1.030-1.176; p=0.004), and Crp ([OR], 1.029; 95% [CI], 1.007-1.051; p=0.01) parameters were found to be independent predictors of mortality. Results of logistic regression analysis related to prognosis of the disease are shown in Table 5.

ROC analysis was performed to find the optimal cut-off value of the *frontal QRS-T angle for predicting mortality.* For the frontal QRS-T angle of ≥ 44.5°, specificity and sensitivity were 93.8% and 84.2%, respectively. (area under curve: 0.937, 95% CI: 0.895–0.979, $p < 0.001$) (Figure 1).

Discussion

In this study, we investigated the ECG changes and the effect of the frontal QRS-T angle on disease severity and prognosis in COVID-19 patients. We found that QT, QTc and frontal QRS-T angle values increased significantly in COVID-19 patients compared to the control group. We also showed that QT, QTc and frontal QRS -T angle values increased significantly as the severity of the disease increased. We also found that frontal QRS-T angle is an independent predictor of disease severity and prognosis. To the best of our knowledge, this is the first study to investigate the effect of frontal QRS-T angle on clinical severity and prognosis in COVID-19 patients.

Previous studies [13-18] reported that CRP, WBC, glucose, urea, and creatinine values increase in COVID-19 patients and are associated with clinical worsening and prognosis. In addition, it was found that the severity of the disease increases and the prognosis worsens as age and SBP increase. In the present study, it was determined that CRP, WBC, glucose, urea and creatinine values increased significantly in the patient group compared to the control group, consistent with the literature. In addition, an increase in disease severity and worsening in prognosis were detected as age increased. We also showed that age is an independent predictor of disease severity.

Although majority of the focus is on the respiratory system in COVID-19 patients, many cardiovascular system complications of this disease have been reported. In addition, previous

studies reported that prognosis is worse in COVID-19 patients with cardiac involvement [4,6-8]. It is inevitable to see ECG abnormalities in these patients with so many cardiac effects.

QT interval is known as the indicator of myocardial repolarization. Since this range is dependent on heart rate, it is usually measured and reported as the corrected QT interval (QTc). Previous studies reported that prolonged QT is associated with ventricular arrhythmias and cardiovascular mortality [19]. It was also reported that QRS time and QT/QTc are increased in COVID-19 patients [20-22]. In the present study, we found that QT/QTc and QRS time increased significantly in the patient group compared to the control group. We also showed that the QT/QTc value increased in correlation with clinical severity.

Calculation of QT and QTc parameters is difficult as it requires additional tools, including a magnifying glass and/or computer programs. In addition, the reproducibility of these parameters is difficult and they are affected by heart rate. Therefore, researchers focused on new parameters that can be easily measured by surface ECG [8,10,23]. Frontal QRS-T angle is defined as the angle between the QRS wave showing ventricular depolarization and the T wave showing ventricular repolarization. This value is defined as a new marker showing ventricular depolarization heterogeneity. In addition, it can be easily measured by subtracting the T wave value from the QRS wave value on the surface ECG. 12-lead ECG devices usually calculate QRS and T wave values automatically [23,24]. In previous publications, it has been reported that the QRS-T angle value is stronger, renewable and less affected by external factors than the QT/QTc value in demonstrating ventricular repolarization [10,23,24]. It has also been reported that the frontal QRS-T angle indicates cardiac risk in patients with myocardial infarction and is a predictor of arrhythmic events in patients with decreased left ventricular function [23,25]. To the best of our knowledge, this is the first study to investigate frontal QRS-T angle and its effects on clinical severity and prognosis in COVID-19 patients. In the present study, it was found that the frontal QRS-T angle is an independent predictor of

clinical severity and prognosis in COVID-19 patients. Moreover, we showed that a cut-off value of ≥ 44.5° for frontal QRS-T angle had 84.2% sensitivity and 93.8% specificity for predicting mortality. Findings of the present study suggest that introduce frontal QRS-T angle to the literature as a new and powerful predictor in determining clinical severity and prognosis in COVID-19 patients.

Limitations

There are certain limitations of this study. The study was designed as a single-center study and the number of patients was limited. Investigation of the relationship between frontal QRS-T angle, cardiac injury markers and cardiac arrhythmia in COVID-19 patients may have contributed to our study. Our findings should be supported by multicenter studies with more patients.

Conclusion

The findings of the present study showed that frontal QRS-T angle can be used as a reproducible, convenient, inexpensive, new and powerful predictor in determining the clinical severity and prognosis of COVID-19 patients.

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Table 1. Demographic and Clinical Characteristics of the Patients

Characteristics	n (%)
Gender	
Male	58 (44.62)
Female	72 (55.38)
Comorbidities	
Hypertension	2 (1.53)
Diabetes mellitus	13 (10)
Heart Failure	12 (9.23)
Chronic respiratory disease	12 (9.23)
Coronary Artery Disease	8 (6.15)
Smoking	20 (15.38)
Symptoms	
Fever	49 (37.69)
Cough	54 (41.54)
Shortness of breath	80 (61.54)
Sore throat	10 (7.69)
Myalgia Fatigue	59 (45.38)
Headache	38 (29.23)
Anorexia	26 (20)
Diarrhea	40 (30.77)
Chest distress	15 (11.54)
Curb-65 Score	
0-1	72 (55.38)
≥2	58 (44.62)
Hospitalization Status	

Outpatient Treatment	45 (34.62)
Normal Service	57 (43.85)
Intensive Care Unit	28 (21.53)
Mortality	
Yes	16 (12.30)
No	114 (87.70)

Table 2. Comparison of Age, Vital Findings, Laboratory and ECG parameters of the Patient and Control Groups

	Patient Group (n=130)	**Control Group (n=100)**	**P Values**
Age (years)	53.44±12.38	51.39±12.70	0.08
SBP (mmHg)	131±21.50	126.95±13.96	<0.001
DBP (mmHg)	77.65±11.83	78.60±9.10	0.14
Pulse (/min)	90.05±20.28	84.71±17.00	0.48
Hgb (g/dL)	12.92±1.66	13.09±1.52	0.66
Glucose (mg/dL)	147.17±87.62	107.06±21.28	<0.001
Wbc ($\times 10^3/\mu$L)	8.35±4.89	7.98±2.44	<0.001
Urea (mg/dL)	44.04±33.23	28.20±11.33	<0.001
Creatinine (mg/dL)	0.90±0.40	0.69±0.19	<0.001
Sodium (mEq/L)	34.77±11.41	135.64±3.18	0.16
Potassium (mEq/L)	4.10±0.55	4.05±0.42	0.15
Crp (mg/L)	54.55±67.86	0.60±1.11	<0.001
QT (msec)	378.07±33.75	368.63±19.65	<0.001
QTC (msec)	410.79±28.19	403.68±11.70	<0.001

QRS Time (msec)	95.04±21.67	91.42±11.08	<0.001
QRS-T Angle (°)	36.57±22.86	22.72±14.08	<0.001

Table 3. Comparison of frontal QRS-T angle and QT/QTc parameters according to clinical severity and survival status of patients

Variables	**1.Grup:CURB-65 <2 (n=72)**	**2.Grup:CURB-65 ≥2 (n=58)**	**P values**
QRS-T angle (°)	32.25 ±18.79	41.94±26.27	0.016
QT (msec)	370.27±25.20	387.75±40.19	0.003
QTC (msec)	402.18±19.92	421.48±33.08	<0.001
	Healing (n=114)	**Exitus (n=16)**	
QRS-T angle (°)	34.22±21.91	53.31±25.19	0.002
QT (msec)	377.06±33.33	385.31±36.95	0.362
QTC (msec)	409.43±26.61	421.43±37.23	0.145

Table 4. Frontal QRS-T angle value; Univariate and multivariate regression analysis showing an independent predictor of clinical severity of COVID-19

	Univariate	**Multivariate**

Variables	OR (95% CI)	P	OR (95% CI)	P
Age	1.204 (1.122-1.293)	<0.001	1.201 (1.111-1.298)	<0.001
QRS-T angle	1.041 (1.021-1.061)	<0.001	1.045 (1.015-1.075)	0.003
Crp	1.017 (1.009-1.025)	<0.001	1.007 (0.996-1.018)	0.185
SBP	0.997 (0.981-1.014)	0.727		
Smoking	0.800 (0.303-2.111)	0.652		
DM	1.510 (0.478-4.768)	0.483		
HT	0.876 (0.312-2.21)	0.752		
Shortness of breath	0.842 (0.412-1.717)	0.635		
Fever	1.281 (0.625-2.626)	0.498		

Table 5. Frontal QRS-T angle value, Univariate and multivariate regression analysis showing an independent predictor of mortality of COVID-19

	Univariate		Multivariate	
Variables	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Age	1.267 (1.086-1.478)	0.003	1.272 (0.865-1.87)	0.221
QRS-T angle	1.077 (1.046-1.108)	<0.001	1.101 (1.030-1.176)	0.004
CRP	1.026 (1.015-1.036)	<0.001	1.029 (1.007-1.051)	0.01
Smoking	6.043 (1.925-18.97)	0.002	0.071 (0.002-2.266)	0.134
QT	1.006 (0.993-1.020)	0.363		

QTc	1.012 (0.996-1.029)	0.149		
DM	1.338 (0.268-6.670)	0.723		
HT	7.533 (0.447-126.84)	0.161		
Shortness of breath	0.329 (0.089-1.219)	0.096		
Fever	0.991 (0.336-2.919)	0.986		

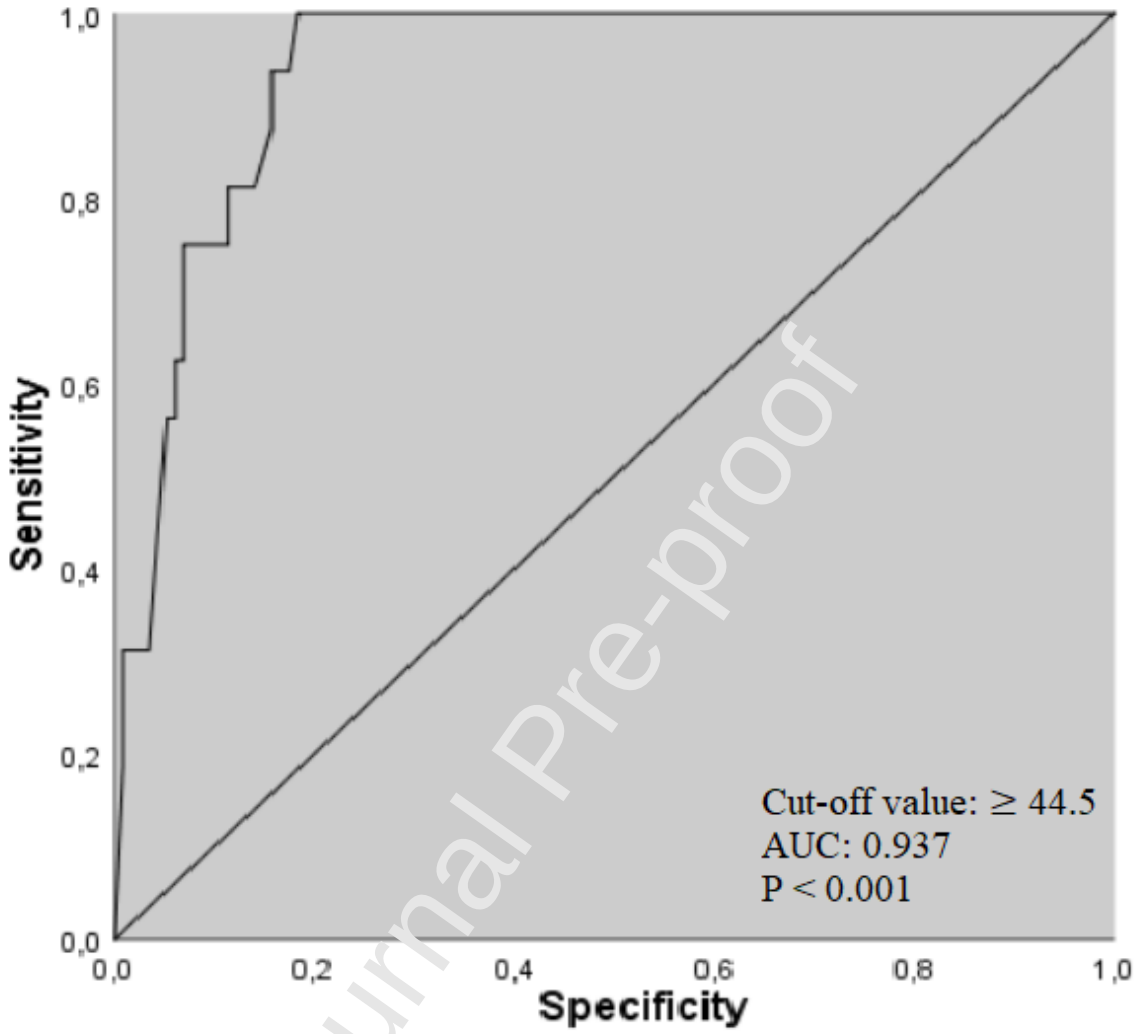

Figure 1. ROC analysis of f(QRS-T) angle

Credit Author Statement

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